CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-144

APPROVAL LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-144

Aventis Pharmaceuticals, Inc.
Attention: Steve Caffé, MD
Senior Vice President and Head
US Regulatory Affairs
200 Crossing Boulevard
P. O. Box 6800
Bridgewater, NJ 08807-0800

Dear Dr. Caffé:

Please refer to your new drug application (NDA) dated February 28, 2000, received March 1, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ketek™ (telithromycin) Tablets, 400 mg.

We acknowledge receipt of your submissions dated:

October 17, 2003	October 27, 2003	October 31, 2003
November 18, 2003	November 26, 2003	December 11, 2003
December 22, 2003	January 8, 2004	January 13, 2004
January 23, 2004	January 26, 2004	January 27, 2004
January 30, 2004	February 2, 2004	February 3, 2004
February 4, 2004	February 5, 2004	February 10, 2004
February 13, 2004	February 16, 2004	February 27, 2004
March 1, 2004	March 4, 2004	March 16, 2004
March 19, 2004	March 23, 2004	March 24, 2004
March 25, 2004	March 26, 2004	March 31, 2004
April 1, 2004		

The October 17, 2003, submission constituted a complete response to our January 24, 2003, action letter.

This new drug application provides for the use of Ketek™ (telithromycin) Tablets for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below, for patients 18 years old and above.

Acute bacterial exacerbation of chronic bronchitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*.

Acute bacterial sinusitis due to *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis* or *Staphylococcus aureus.*

Community-acquired pneumonia (of mild to moderate severity) due to *Streptococcus pneumoniae* (including multi-drug resistant *Streptococcus pneumoniae* [MDRSP] strains), *Haemophilus influenzae, Moraxella catarrhalis, Chlamydophila pneumoniae,* or *Mycoplasma pneumoniae.*

We completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text included with this letter.

The final printed labeling (FPL) must be identical to enclosed labeling (text for the package insert, patient package insert, and immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA.* Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-144.**" Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirements for acute exacerbation of chronic bronchitis for all pediatric ages. We are deferring submission of your pediatric studies for ages less than 18 years for acute bacterial sinusitis and community-acquired pneumonia until March 31, 2008.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required post-marketing commitments. The status of post-marketing commitments shall be reported annually according to 21 CFR 314.81. These commitments are listed below:

1. Information to support the pediatric use of telithromycin for the treatment of acute bacterial sinusitis in pediatric patients ages less than 18 years of age.

   Final Report Submission: March 31, 2008

2. Information to support the pediatric use of telithromycin for the treatment of community-acquired pneumonia in pediatric patients ages less than 18 years of age.

   Final Report Submission: March 31, 2008

Submit final study reports to this NDA. For administrative purposes, all submissions related to these pediatric post-marketing commitment(s) must be clearly designated "**Required Pediatric Study Commitments**".

In addition, we remind you of your post-marketing commitment in your submission dated April 1, 2004. This commitment is listed below

3. Submit an updated assessment of all post-marketing visual adverse events that are reported globally for the first eighteen months after U.S. launch. This assessment will include detailed information regarding the nature of the visual adverse event, duration, resulting sequelae, if any, and description of any formal diagnostic evaluations to assess this event. Particular attention will be paid to patients whose symptoms did not resolve promptly. Information on the patients in question including but not limited to underlying diseases and concomitant medications will also be submitted.

   Final Report Submission: March 31, 2006

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence**."

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

The Agency emphasizes the importance of describing the visual adverse effects of telithromycin in promotional materials to provide fair balance to promotional claims.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Judit Milstein, Regulatory Project Manager at (301) 827-2207.

Sincerely,

{See appended electronic signature page}

Mark Goldberger, MD, MPH
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure: Package Insert
Patient Package Insert
Carton and Container Labeling

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APPLICATION NUMBER:

21-144

APPROVABLE LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-144

Aventis Pharmaceuticals Inc
Attention: Gillian Ivers-Read, B.Sc.
Vice President
Global Drug Regulatory Affairs
Route 202-206
P.O. Box 6800
Bridgewater, NJ 08807-0800

Dear Ms. Ivers-Read:

Please refer to your new drug application (NDA) dated February 28, 2000, received March 1, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for KETEK™ (telithromycin) 400 mg. Please note that for administrative purposes, we have assigned a new NDA number (NDA 21-391) to the Tonsillitis/Pharyngitis indication. Our response to this proposed indication is addressed in a separate letter.

We acknowledge receipt of your submissions dated:

March 23, 2000	April 5, 200	April 11,2000	April 13, 2000	April 14, 2000
April 20, 2000	May 4, 2000	June 1, 2000	June 2, 2000	June 21, 2000
June 22, 2000	June 29, 2000	June 30, 2000	July 5, 2000	July 6, 2000
July 10, 2000-2	July 13, 2000	July 19, 2000	July 21, 2000	July 28, 2000
August 4, 2000	August 7, 2000-2	August 8, 2000	August 11, 2000	August 12, 2000
August 16, 2000	August 24, 2000	August 29, 2000	August 30, 2000	August 31,2000-2
Sept. 1, 2000-2	Sept. 7, 2000	Sept. 8, 2000	Sept. 11, 2000	Sept. 13, 2000
Sept. 14, 2000	Sept. 19, 2000-2	Sept. 20, 2000-2	Sept. 28, 2000	Sept. 29, 2000-2
October 2, 2000	October 3, 2000	October 4, 2000	October 6, 2000	October 19, 2000
October 20, 2000-2	October 23, 2000	October 24, 2000	October 25,2000	October 27, 2000
October 31, 2000-2	Nov. 2, 2000-2	Nov. 3, 2000-2	Nov.7, 2000	Nov. 8, 2000
Nov. 13, 2000	Nov. 15, 2000	Nov. 16, 2000-2	Nov. 17, 2000	Nov. 20, 2000
Nov. 28, 2000	Nov. 29, 2000	Nov. 30, 2000	Dec. 1, 2000	Dec. 4, 2000
Dec. 5, 2000-2	Dec. 7, 2000	Dec. 12, 2000	Dec. 14, 2000	Dec. 18, 2000
Dec. 20, 2000	Dec. 21, 2000-2	January 3, 2001	January 4, 2001-2	January 10, 2001
January 12, 2001	January 17, 2001	January 19, 2001(2)	January 22, 2001	January 24, 2001
January 25, 2001	January 26, 2001	January 31, 2001	February 1, 2001	February 7, 2001
February 14, 2001	February 15, 2001	February 16, 2001-2	February 20 ,2001-3	February 21, 2001
February 26, 2001	February 27, 2001-2	February 28, 2001	March 1, 2001	March 2, 2001
March 9, 2001	March 12, 2001	March 16, 2001-2	March 19, 2001	March 20, 2001-2
March 21, 2001-4	March 22, 2001	March 23, 2001-2	March 24, 2001	March 28, 2001
March 29, 2001-3	April 3, 2001-2	April 4, 2001	April 6, 2001	April 10, 2001
April 17, 2001-2	April 18, 2001	April 20, 2001	April 27, 2001-2	May 1, 2001
May 24, 2001				

We have completed the review of this application for Community-Acquired Pneumonia (CAP), Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB), and Acute Bacterial Sinusitis (ABS), as amended, and it is approvable. However, the data are insufficient in your NDA to assess fully the potential risks posed by the concentration-related effect of telithromycin on cardiac repolarization, hepatotoxicity, and drug exposure in patients with renal and/or hepatic impairment. Finally, the differences in the cause of mortality in the telithromycin treatment groups versus comparators are of concern.

Before this application may be approved, it will be necessary for you to address the following:

Clinical Studies Targeting Resistant Pathogens

You should conduct a large clinical study of CAP/ABS in order to capture further patients with *S. pneumoniae* isolates resistant to penicillin and/or erythromycin, and beta-lactamase producing strains of *H. influenzae*. Within this large database, monitoring and analysis of adverse event reports, including hepatic, cardiac (QT interval) and visual adverse events, are highly recommended in order to obtain a larger safety database upon which to assess the benefit/risk profile.

- Penicillin-resistant *S. pneumoniae* (PRSP) and erythromycin-resistant *S. pneumoniae* (ERSP): Based on our review of the clinical data submitted in your NDA, we have concluded that insufficient data were provided for the treatment of community-acquired pneumonia (CAP) of mild to moderate severity and acute bacterial sinusitis (ABS) due to PRSP and ERSP.

- Acute Bacterial Sinusitis (ABS): Before we would be prepared to approve a PRSP or ERSP claim for ABS, you should establish clinical efficacy of telithromycin against PRSP in a more serious indication (e.g., CAP).

Safety and Clinical Pharmacology:

1. It would be helpful to conduct a phase III study of CAP/ABECB/ABS to assess further adverse events associated with telithromycin, particularly in patients at increased risk for potential drug-related toxicity. Such a study should be randomized, with at least 35% of the recruited study population consisting of patients 50 years of age and older. Exclusion criteria regarding concomitant medications should be minimized. Recruitment of patients with renal and/or hepatic impairment is encouraged. This study should include the monitoring and analysis of all adverse events, with particular attention to hepatic, visual, cardiovascular, and vasculitic adverse events. Investigations of any mortality outcomes by investigators should be conducted to evaluate optimally possible cardiac or liver toxicities or evidence of systemic vasculitis.

2. Investigate the steady-state pharmacokinetics of telithromycin following administration of 400 mg, 600 mg and 800 mg once daily to patients with mild, moderate, and severe renal impairment in order to provide dose adjustment recommendations for the product label. Blood should be sampled at multiple time-points to assay for telithromycin. Electrocardiograms should be obtained at the time of each blood sample and analysis of changes in QT interval duration performed.

3. Investigate the effect of co-administration of ketoconazole on the steady-state pharmacokinetics

of telithromycin following administration of 800 mg once daily to elderly patients with mild to moderate renal impairment. This information is necessary to characterize drug exposure in patients at potentially greater risk due to multiple perturbations of drug elimination pathways. Blood should be sampled at multiple time-points to assay for telithromycin. Electrocardiograms should be obtained at the time of each blood sample and analysis of changes in QT interval duration performed.

4. Conduct an *in vitro* study (or studies) to investigate the drug metabolism of RU 76363 including an assessment of the potential effect of RU 76363 on IKr. Telithromycin and some other anti-infectives should be used as comparators (e.g., clarithromycin, moxifloxacin, and levofloxacin).

5. The visual blurring reported in the clinical studies is not currently well understood or adequately studied. It may be a signal for a more serious condition such as angle closure glaucoma or retinal toxicity. Additional clinical studies are recommended to address telithromycin's effect on visual acuity, refraction, accommodation, anterior chamber angle, lens, pupil dilation, tear film stability, visual field (threshold automated testing), and color vision.

General Comments:

1. Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB): Your current application regarding *H. influenza* and M. *catarrhalis* is insufficient due to low numbers of isolates.

Please note that revised draft labeling is not being provided at this time. Further revisions to the submitted label will be required before this application can be approved.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA, may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Jose R. Cintron, R.Ph., M.A., Sr. Regulatory Management Officer/Project Manager, at (301) 827-2125.

Sincerely,

{See appended electronic signature page}

Dianne Murphy, M.D.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dianne Murphy
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